VERIFICATION OF A TRANSLATION

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declare as follows:

1. That I am well acquainted with both the English and Japanese languages

2. That the attached document is a true and correct translation made by me to the best of my knowledge and belief of:-

The specification accompanying the Application No. 2003-179077

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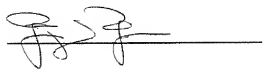
filed on June 24, 2003

Date

Signature of the translator

August 14, 2008



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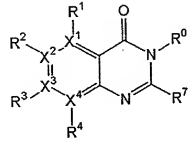
SPECIFICATION

[Title of the invention]

Method for preparing pyrimidin-4-one compounds

[Scope of patent claim]

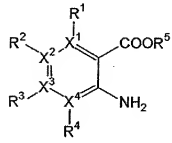
1. A method for preparing a pyrimidin-4-one compound having the formula (4):



(4)

(in which each of $X^1$, $X^2$, $X^3$ and $X^4$ independently represents a carbon atom or a nitrogen atom (provided that not all of them are carbon atoms at the same time); $R^0$ represents a hydrogen atom or a hydrocarbyl group; each of $R^1$, $R^2$, $R^3$ and $R^4$ is independently present only when each of $X^1$, $X^2$, $X^3$ and $X^4$, respectively, is a carbon atom, and if present, each of $R^1$, $R^2$, $R^3$ and $R^4$ independently represents a group which optionally has a substituent and which does not participate in the reaction, provided that $R^1$, $R^2$, $R^3$ and $R^4$ are the same as or different from each other and that $R^1$, $R^2$, $R^3$ and $R^4$ can form a ring in combination; and $R^7$ has the same meaning defined as $R^1$, $R^2$, $R^3$ and $R^4$);

which comprises reacting a heteroarylaminocarboxylic acid compound having the formula (2):



(2)

(in which each of $X^1$, $X^2$, $X^3$, $X^4$, $R^1$, $R^2$, $R^3$ and $R^4$ has the same meaning defined as above, and $R^5$ represents hydrogen or a hydrocarbyl group);
with an organic acid compound having the formula (3):

$$(R^6O)_3CR^7 \qquad (3)$$

(in which $R^6$ represents a hydrocarbyl group, and $R^7$ has the same meaning defined as above);
in the presence of an amine compound having the formula (1):

$$R^0NH_2 \qquad (1)$$

(in which $R^0$ has the same meaning defined as above).

2. The method of claim 1 for preparing a pyrimidin-4-one compound, in which $R^6$ is methyl or ethyl.

[Detailed description of the invention]
[Field of the invention]

This invention relates to a method for preparing pyrimidin-4-one compounds from heteroarylaminocarboxylic acid compounds. The pyrimidin-4-one compounds are useful compounds as starting compounds or intermediate compounds for preparing pharmaceutically active chemical compounds and agricultural chemical compounds.

[Prior art]

As a method for preparing a pyrimidin-4-one compound from a heteroarylaminocarboxylic acid compound, it is disclosed (for example, in Non-patent Document 1) that 3-benzyl-2-butyl-3H-pyrido[3,2-d]pyrimidin-4-one hydrochloride is obtained with a yield of 8% by reacting 3-amino-2-pyridinecarboxylic acid with pentanoic acid anhydride at 140°C and further reacting the reaction product with

benzylamine at 200°C. However, this method has problems in that complicated operations are required because of the reactions at very high temperatures and in that the product is obtained with a low yield, and accordingly is not suitable for industrial production of pyrimidin-4-one compounds.

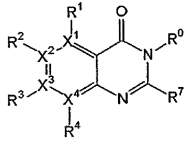
Non-patent Document 1: J. Med. Chem., 41, 4021(1998) (pp. 4033, Experiments)

[Problem to be solved by the invention]

The present invention has an object to solve the above problems and to provide such an industrially suitable method for preparing pyrimidin-4-one compounds that the pyrimidin-4-one compounds can be easily prepared from heteroarylaminocarboxylic acid compounds with high yields under simple and moderate conditions.

[Means to solve the problem]

The object of the present invention is achieved by a method for preparing a pyrimidin-4-one compound having the formula (4):

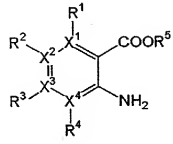


(4)

(in which each of $X^1$, $X^2$, $X^3$ and $X^4$ independently represents a carbon atom or a nitrogen atom (provided that not all of them are carbon atoms at the same time); $R^0$ represents hydrogen or a hydrocarbyl group; each of $R^1$, $R^2$, $R^3$ and $R^4$ is independently present only when each of $X^1$, $X^2$, $X^3$ and $X^4$, respectively, is a carbon atoms, and if present, each of $R^1$, $R^2$, $R^3$ and $R^4$ independently represents a

group which optionally has a substituent and which does not participate in the reaction, provided that $R^1$, $R^2$, $R^3$ and $R^4$ are the same as or different from each other and that $R^1$, $R^2$, $R^3$ and $R^4$ can form a ring in optional combinations; and $R^7$ has the same meaning defined as $R^1$, $R^2$, $R^3$ and $R^4$);

which comprises reacting a heteroarylaminocarboxylic acid compound having the formula (2):



(2)

(in which each of $X^1$, $X^2$, $X^3$, $X^4$, $R^1$, $R^2$, $R^3$ and $R^4$ has the same meaning defined as above, and $R^5$ represents hydrogen or a hydrocarbyl group);

with an organic acid compound having the formula (3):

$$(R^6O)_3CR^7 \qquad (3)$$

(in which $R^6$ represents a hydrocarbyl group, and $R^7$ has the same meaning defined as above);

in the presence of an amine compound having the formula (1):

$$R^0NH_2 \qquad (1)$$

(in which $R^0$ has the same meaning defined as above).

[Embodiment of the invention]

The amine compound used in the reaction of the present invention is represented by the above formula (1). In the formula (1), $R^0$ represents hydrogen or a hydrocarbyl group. Examples of the hydrocarbyl group are

alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; aralkyl groups such as benzyl, phenethyl, and phenylpropyl; and aryl groups such as phenyl, p-tolyl, naphthyl, and anthryl. These groups can be in any isomer forms.

The aforementioned amine compound can be employed preferably in an amount of 1 to 100 moles, more preferably in an amount of 3 to 40 moles, per one mole of the heteroarylaminocarboxylic acid compound. The amine compound can be in any of gas, liquid, and solid. Otherwise, the compound can be employed in a solution in an organic solvent such as a polar solvent (e.g., alcohol).

The heteroarylaminocarboxylic acid compound used in the reaction of the invention is represented by the above formula (2). In the formula (2), each of $R^1$, $R^2$, $R^3$ and $R^4$ is independently present only when each of below-described $X^1$, $X^2$, $X^3$ and $X^4$, respectively, is a carbon atom. If present, each of $R^1$, $R^2$, $R^3$ and $R^4$ independently represents a group which optionally has a substituent and which does not participate in the reaction, and they are the same as or different from each other. Examples of them include hydrogen atom, alkyl groups, cycloalkyl groups, aralkyl groups, aryl groups, halogen atoms, hydroxyl group, alkoxy groups, alkylthio groups, nitro group, cyano group, carbonyl group, amino groups (which cannot be used as $R^1$), and carboxyl group (which cannot be used as $R^4$). $R^1$, $R^2$, $R^3$ and $R^4$ can form a ring in optional combinations.

The alkyl groups can be methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, or decyl. These groups can be in any isomer forms.

The cycloalkyl groups can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl.

The aralkyl groups can be benzyl, phenethyl, or phenylpropyl. These groups can be any isomer forms.

The aryl groups can be phenyl, p-tolyl, naphthyl, or anthryl. These groups can be in any isomer forms.

The halogen atoms can be fluorine, chlorine, bromine, or iodine.

The alkoxy groups can be methoxy, ethoxy, or propoxy. These groups can be in any isomer forms.

The alkylthio groups can be methylthio, ethylthio, or propylthio. These groups can be in any isomer forms.

The alkyl groups, cycloalkyl groups, aralkyl groups, aryl groups, alkoxy groups, alkylthio groups and amino groups (which cannot be used as $R^1$) can have a substituent. The substituent can be a substituent connected via a carbon atom, a substituent connected via an oxygen atom, a substituent connected via a nitrogen atom, a substituent connected via a sulfur atom, or a halogen atom.

Examples of the substituents connected via a carbon atom include alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, and hexyl, cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclobutyl, alkenyl groups such as vinyl, allyl, propenyl, cyclopropenyl, cyclobutenyl, and cyclopentenyl, heterocyclic groups such as pyrrolidyl, pyrrolyl, furyl, and thienyl, aryl groups such as phenyl, tolyl, xylyl, biphenylyl, naphthyl, anthryl, and phenanthryl, acyl groups (which can be acetallized) such as formyl, acetyl, propionyl, acryloyl, pivaloyl, cyclohexylcarbonyl, benzoyl, naphthoyl, and toluoyl, carboxyl groups (which cannot be used as $R^4$), alkoxycarbonyl groups (which cannot be used as $R^4$) such as methoxycarbonyl and ethoxycarbonyl, aryloxycarbonyl groups (which cannot be used as $R^4$) such as phenoxycarbonyl, halogenated alkyl groups such as trifluoromethyl, and cyano group. These groups can be in any isomer forms.

Examples of the substituents connected via an oxygen atom include hydroxyl group, alkoxy groups such as methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, benzyloxy, piperidyloxy, and pyranyloxy, and aryloxy groups such as phenoxy, tolyloxy, and naphthyloxy. These groups can be in any isomer forms.

Examples of the substituents connected via a nitrogen atom include primary amino groups such as methylamino, ethylamino, butylamino, cyclohexylamino, phenylamino, and naphthylamino, secondary amino groups such as dimethylamino, diethylamino, dibutylamino, methylethylamino, methylbutylamino, and diphenylamino, heterocyclic amino groups such as morpholino, thiomorpholino, piperidino, piperazinyl, pyrazolidinyl, pyrrolidino, and indolyl. These groups can be in any isomer forms.

Examples of the substituents connected via a sulfur atom include mercapto group, thioalkoxy groups such as thiomethoxy, thioethoxy, and thiopropoxy, and thioaryloxy groups such as thiophenoxy, thiotolyloxy and thionaphthyloxy. These groups can be in any isomer forms.

Examples of the halogen atoms include fluorine, chlorine, bromine, and iodine.

$R^5$ represents hydrogen or a hydrocarbyl group. Examples of the hydrocarbyl group are alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, and hexyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; aralkyl groups such as benzyl, phenethyl, and phenylpropyl; and aryl groups such as phenyl, tolyl, naphthyl, and anthryl. These groups can be in any isomer forms.

The organic acid compound used in the reaction of the invention is represented by the above formula (3). In the formula (3), $R^6$ represents hydrogen or a hydrocarbyl group. Examples of the hydrocarbyl group are alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl; cycloalkyl groups

such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; aralkyl groups such as benzyl, phenethyl, and phenylpropyl; and aryl groups such as phenyl, p-tolyl, naphthyl, and anthryl. Alkyl groups are preferred, and methyl and ethyl are more preferred. These groups can be in any isomer forms

$R^7$ has the same meaning defined as $R^1$, $R^2$, $R^3$ and $R^4$, and each of $X^1$, $X^2$ and $X^3$ independently represents a carbon atom or a nitrogen atom (provided that not all of $X^1$, $X^2$, $X^3$ and $X^4$ are carbon atoms at the same time).

The aforementioned organic acid compound can be employed preferably in an amount of 1.0 to 15 moles, more preferably in an amount of 1.1 to 5.0 moles, per one mole of the heteroarylaminocarboxylic acid compound.

The reaction of the invention can be carried out in the presence or absence of a solvent. There are no specific limitations with respect to the solvents, under the condition that the solvent does not give adverse effect to the reaction. Examples of the solvents include alcohols such as methanol, ethanol, isopropyl alcohol, n-butyl alcohol, t-butyl alcohol, and n-pentanol, amides such as N,N-dimethylformamide and N-methylpyrrolidone, ureas such as N,N'-dimethylimidazolidinone, sulfoxides such as dimethyl sulfoxide, aromatic hydrocarbons such as benzene, toluene, xylene, and mesitylene, halogenated aliphatic hydrocarbons such as methylene chloride, chloroform, and dichloroethane, nitriles such as acetonitrile and propionitrile, and ethers such as diethyl ether, tetrahydrofuran, and dioxane. Preferred are alcohols, amides, and nitriles. More preferred are methanol, ethanol, N,N'-dimethylimidazolidinone, and acetonitrile. The solvents can be used singly or in combination.

The solvent can be employed preferably in an amount of 0 to 50 g, more preferably 0 to 20 g, most preferably 0 to 5 g, per 1 g of the heteroarylaminocarboxylic acid compound. The amount may vary depending on the condi-

tions of the liquid reaction mixture such as homogeneousness and/or easiness for stirring.

The reaction of the invention can be carried out by mixing and stirring the amine compound, heteroarylamino-carboxylic acid compound, organic acid compound, and solvent under inert gas atmosphere. The temperature for the reaction is preferably in the range of 40 to 200°C, more preferably 50 to 150°C. There is no limitation on pressure for the reaction.

The final product, i.e., the pyrimidin-4-one compound, can be isolated and purified after completion of the reaction by known methods such as extraction, filtration, concentration, distillation, recrystallization, and/or column chromatography.

[Examples]

The invention is further described by the following example, but it by no means restricts the present invention.

[Example 1] Synthesis of 3H-pyrido[2,3-d]pyrimidin-4-one

In a pressure resistant, 10 mL-volume stainless steel vessel, 1.00 g (7.2 mmol) of 2-aminonicotinic acid, 3.07 g (28.8 mmol) of methyl orthoacetate, and 5.0 mL (38 mmol) of 15 wt.% ammonia-methanol solution were heated at 105°C for 8 hours for performing a reaction. After the reaction was complete, the reaction mixture was cooled to room temperature and concentrated under reduced pressure, to give 1.06 g (yield after isolation: 100%) of 3H-pyrido[2,3-d]pyrimidin-4-one as a black solid product.

The 3H-pyrido[2,3-d]pyrimidin-4-one had the following properties:

$^1$H-NMR (DMSO-$d_6$, $\delta$(ppm)): 3.36 (1H, brs), 7.46 (1H, dd, J=8.0, 4.5 Hz), 8.31 (1H, s), 8.45 (1H, dd, J=7.8, 2.1 Hz), 8.87 (1H, dd, J=4.8, 2.1 Hz)

CI-MS (m/e): 148 (M+1)

[Effect of the invention]

The present invention can provide an industrially suitable method for preparing pyrimidin-4-one compounds. According to the invention, pyrimidin-4-one compounds can be easily prepared from heteroarylaminocarboxylic acid compounds with high yields under simple and moderate conditions.